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Clinical Investigation

Stereotactic radiosurgery for the treatment and palliation of base of skull metastases

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OBJECTIVES: Patients with skullbase metastases often present with evolving cranial nerve deficits, pain and advanced systemic disease. These factors along with declining performance status limit invasive interventions; yet, a safe, efficient treatment modality that augments palliative efforts is desirable. We herein report the role of stereotactic radiosurgery (SRS) in the management of base of skull metastases.

METHODS: This retrospective institutional series reviewed 18 consecutive patients (12 male, 6 female) with of a total of 21 skullbase metastases. Seventy-five percent of patients presented with symptomatic disease most commonly consisting of pain, specific cranial nerve involvement included trigeminal (3), abducens (1), facial (2), and vestibulocochlear (3) nerves. The median prescribed dose was 18 Gy (range 15-40) with eleven of the treatments delivered as a single fraction consisting of 15-21 Gy and the most common fractionated regimen being 24 Gy delivered in 3 fractions.

RESULTS: Of the eighteen patients, 10 were transitioned to hospice care and succumbed to extensive metastatic disease prior to the first imaging evaluation. Clinical and imaging follow-up demonstrated local failure in 3/8 of the remaining patients. In regards to palliation of symptoms, 5/6 of the patients with significant cranial nerve deficits reported improvement in symptoms within 1 month. Additionally, 5/5 patients with pre-treatment pain reported improvement.

CONCLUSIONS: SRS is a safe, efficient, and potentially effective treatment for skullbase metastases with acceptable rates of local control. SRS leads to improvement in both pain and cranial nerve deficits and should therefore be integrated into the multidisciplinary palliation of this unique patient population.

KEYWORDS: Base of skull, metastases, radiation therapy, stereotactic radiosurgery, palliative care, cranial nerves

1 INTRODUCTION

Metastases to the base of skull from distant sites can be a particularly problematic manifestation of metastatic disease, often resulting in craniofacial pain and evolving constellations of cranial nerve deficits [1]. Base of skull metastases can occur as the first presentation of malignancy but more often occur later in the course of illness when systemic disease is already extensive [2,3]. Treatment options consist of chemotherapy, surgery and radiation therapy including conventional radiotherapy as well as stereotactic radiosurgery (SRS). Surgical resection of base of skull tumors, when appropriate, can be complicated by involvement of neurovascular structures which results in increased morbidity and mortality [4]. Radiotherapy has been shown to be

very effective in amelioration of cranial nerve deficits, particularly when given early after onset of symptoms [1,5]. Nonetheless, standard external beam therapy inevitably results in treatment of large volumes that may encompass cranial nerve pathways that are sensitive to radiation [6,7]. Additionally, conventional treatment is delivered in 10 to 14 fractions requiring daily facility visits of patients with poor performance status or prolonged hospitalization. SRS is an attractive treatment modality in this setting given its ability to deliver higher doses of radiation in a more conformal manner with favorable dose fall-off that may spare surrounding vulnerable structures in one or a minimal number of treatments. Herein, we retrospectively assess the efficacy and safety of linac-based SRS for treatment and palliation of cranial base metastases.

2 MATERIALS AND METHODS

2.1 Patient Population

We identified 18 patients with 21 base of skull metastases treated with SRS between January 2001 and December 2011. Six patients (33%) were female and 12 patients (66%) were male. The median age was 65 years (range: 35-78) presenting at a median of 43 months (range: 4.2-188) following the primary diagnosis, which consisted of melanoma (4), kidney (4), lung (3), breast (4), prostate (2), and colon (1) cancers. The median Karnofsky performance status (KPS) at time of treatment was 70 (range: 50-90). The median total number of intracranial metastases per patient was 2 (range: 1-5). While 75% of patients presented with symptomatic disease most commonly consisting of pain, specific cranial nerve involvement included trigeminal (3), abducens (1), facial (2), and vestibulocochlear (3) nerves. No patients had previously undergone whole brain radiation (WBRT) although one patient underwent sequential WBRT + SRS.

2.2 SIMULATION AND PLANNING

Each patient was comfortably positioned on the CT simulation table and a custom mask was fabricated. A thin-slice high resolution CT with intravenous contrast was then obtained while the patient was immobilized. The acquired images were then transferred to the treatment planning workstation and fused with pre-treatment thin-slice (1.2 mm) contrast enhanced spoiled gradient recalled acquisition in steady state (SPGR) sequence MRI utilizing commercially available fusion software. The tumor volume and any nearby critical structures were manually delineated by a team including a radiation oncologist, a medical physicist, and a neurosurgeon. The planning target volume (PTV) was defined as the contrast-enhancing tumor on MRI with no margin. Dose-volume histograms were calculated for the target volume as well as nearby critical structures and were utilized to select the optimal treatment plan. An ideal SRS plan provided 95% of the prescription dose to the PTV while sparing surrounding organs at risk. If surrounding organs at risk were deemed to be at excess risk for toxicity, a plan with lower PTV coverage was accepted. Radiosurgery was performed using Cyber Knife™ Robotic Radiosurgery System (Accuray, Inc, Sunnyvale, CA) for 17 patients and TrilogyTM Radiosurgery System (Varian Medical Systems, Palo Alto, CA) for one patient.

2.3 Follow-up

Follow-up neurologic exam and MRI (or CT scanning if ineligible for MRI) were performed at 2 months after SRS, every 2-3 months for the 1st year, and at 3 to 6 monthly intervals thereafter. Imaging was performed to assess changes in tumor size, to identify the development of any new tumors, and to evaluate the risk of peritumoral reactive swelling. A significant change in tumor size was defined as either an increase or decrease of 2 mm in the contrast-enhancing dimensions in any single plane of the tumor. Distant failure was defined as the development of new brain metastases outside the original SRS treatment volume.

2.4 Statistics

Survival time was computed from the time of SRS. Survival curves and median survival were calculated using the Kaplan–Meier method [8]. Factors affecting survival from the time of brain metastasis diagnosis were determined using the Cox proportional hazards model [9]. All statistical tests were carried out using SPSS Version 15.0 (SPSS, Chicago, IL. Research was done under an approved University of Pittsburgh Institutional Review Board IRB.

3 RESULTS

A total of 21 tumors were treated in 18 patients. The median radiosurgery tumor volume was 2.9 cm^3 (range 0.3-71 cm^3) with a median prescription dose of 18 Gy (range: 15-40 Gy) delivered in 1- 5 fractions

to the 80% isodose line. Eleven tumors (52%) were treated in a single fraction, 7 in three fractions (33%), and 3 in five fractions (14%). Dose selection and fractionation was based on various factors including performance status, tumor volume, location, timing and total dose of prior radiation therapy. The median minimum tumor dose was 13.9 Gy (range: 6.3-23.5 Gy) and the median tumor coverage was 95% (range: 55-100%).

Of the 18 patients, 10 succumbed to extensive metastatic disease prior to the first imaging evaluation. Clinical and imaging follow-up was available for the 8 remaining patients. Three patients had local failure 1.2, 2.5, and 5.4 months following treatment corresponding to a 6-month local control rate of 63% (Figure 1). No significant predictors for local control were found.

At the time of this analysis, 15 of 18 patients had died; however, only one succumbed from progressive CNS disease. The median overall survival was 1.8 months with a 6 month overall survival rate of 22% (Figure 2). On Cox regression analysis, RPA ($p < 0.05$) and KPS ($p < 0.05$) were found to be significant predictors of improved survival.

Of the 8 subjects with available imaging follow-up, 6 subjects (75%) developed distant intracranial metastases with a 6-month distant intracranial control rate of 16% and a median time to distant metastasis of 2.2 months.

In regards to palliation of symptoms, 6 of the patients had significant cranial nerve deficits of which 5 (83%) reported improvement in symptoms prior to the first clinical evaluation 1 month following treatment. Additionally, all 5 patients with pre-treatment pain reported an improvement (100%). One patient reported an increase in paraesthesias and periorbital edema, which improved with a short-course of dexamethasone.

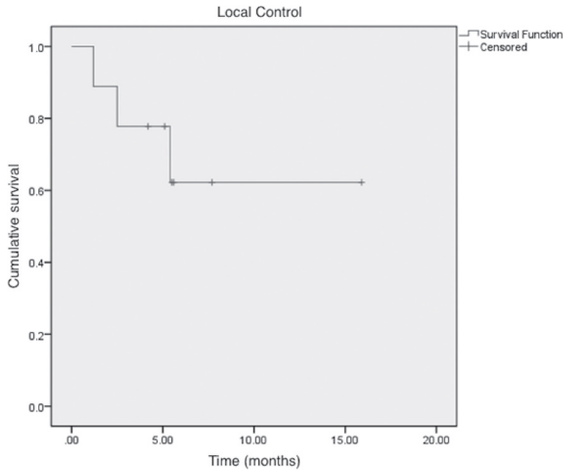

Figure 1. Kaplan-Meier analysis of local control after SRS for base of skull metastases. The 6-month local control rate was 62.5%.

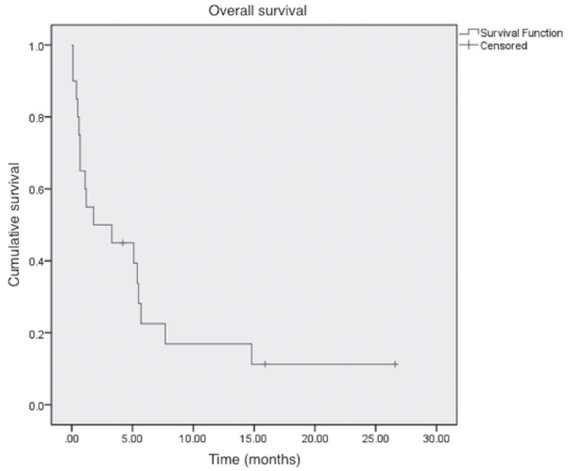

Figure 2. Kaplan-Meier analysis of overall survival after SRS for base of skull metastases. The 6-month overall survival was 22% with a median overall survival of 1.8 months.

4 DISCUSSION

Metastases to the base of skull are a difficult problem to manage given their inaccessible location, association with cranial nerve deficits and even poorer prognosis when these symptoms occur [10-13]. In this report, we describe the use of SRS for management of base of skull metastases and demonstrate high rates of symptom and pain relief as well as a reasonable rate of local control. Furthermore, we have shown that this treatment can be delivered in a single or minimal number of treatments while being relatively safe, rarely resulting in adverse effects that are mild when they do occur.

The reports examining SRS for base of skull metastases are limited (Table 2). Mori et al. [14] examined 11 patients with cranial base metastases that were treated with stereotactic radiotherapy to 30-50 Gy in 10-14 fractions. They found an overall control rate of 100% with symptom improvement in 10/11 subjects and median survival time of 16 months. The authors argue that Linac-based SRS may provide an important advantage over Gamma Knife SRS by utilizing higher isodose resulting in lower maximum doses that may spare cranial nerve structures that are embedded in the treatment volume.

Kano et al. [6] assessed the use of Gamma Knife for management of 37 patients with metastases or

Table 1. Characteristics of patients receiving SRS for base of skull metastases

Characteristic	Value
Patients (F/M), n	18 (6/12)
Lesions, n	21
Median age (range), y	65 (35-78)
Primary Malignancy, n (%)	
Melanoma	4 (22%)
Renal	4 (22%)
Breast	4 (22%)
Lung	3 (17%)
Prostate	2 (11%)
Colon	1 (6%)
Cranial nerve deficits, n (%)	
Trigeminal	3 (17%)
Abducens	1 (6%)
Facial	2 (11%)
Vestibulocochlear	3 (17%)
Median KPS score (range)	70 (50-90)
RPA class, n (%)	
I	1 (6%)
II	15 (83%)
III	2 (11%)
Number of intracranial metastases at time of SRS, n (%)	
1	8 (44%)
2 to 4	7 (39%)
>4	1 (6%)
Median interval between primary diagnosis and SRS (range), mo	43 (4-189)
Median tumor volume (cc), range	2.9 (0.3-71)
Median SRS dose (range), Gy	18 (15-40)
Treatment Schemes (Gy/ Fractions), n (%)	
15-18 / 1	11 (52%)
18-24 / 3	7 (33%)
20-40 / 5	3 (14%)
Treatment Modality, n (%)	
Cyberknife	17 (94%)
Trilogy	1 (6%)

direct invasion of adjacent malignancies to the cavernous sinus with a median lesion size of 6.3 cm^3. Using a median dose of 14 Gy delivered in a single fraction, they found the median survival to be 8.9 months with a 78% rate of local control, symptomatic improvement in 35% of subjects and no adverse effects. Based on these results, SRS was determined to be an effective treatment for palliation of metastases and extensions to the cavernous sinus, particularly when treatment was given earlier after diagnosis.

Multiple other studies have investigated the use of SRS for management of primary malignancies of the base of skull or extension of tumors from head and neck structures to the skull base using SRS with promising results [4,15,16]. These findings, however, are likely not directly applicable to the management of secondary metastases. Patients with base of skull metastases from distant sites often present later in the course of illness when there is more likely to be active systemic disease [1]. Furthermore, these patients may be presenting with metastasis from primary malignancies of radioresistant histologies, as was the case in our series where 44% of patients presented with melanoma or renal cell carcinoma. As such, analysis of outcomes assessing SRS for primary malignancies of the skull base cannot extend to the management of metastases to the base of skull from distant sites where the burden of disease is higher and prognosis is expected to be significantly worse. Additionally, primary malignancies of the skull base more frequently result in cranial nerve deficits that are not as responsive to radiation therapy whereas neurological function can often be restored or improved when they are due to metastases from distant organs [17].

In the present study, we found the median overall survival to be 1.8 months with lower RPA and lower KPS predicting shorter survival. This is the first study to find characteristics that may predict outcomes in patients with base of skull metastases from distant sites treated with SRS. Other studies assessing SRS for cavernous sinus metastases and invasions have demonstrated that advanced age [18] and the presence of systemic metastases are associated with worse outcomes [18,19]. While the identification of such predictors is critical for the evaluation and stratification of potential candidates for SRS, the main focus is to improve symptoms in a safe, efficient manner as part of a coordinated palliative care effort.

Most importantly, our data demonstrate that in patients with available follow-up data, the rate of cranial nerve symptom improvement was 83% and the

Table 2. Studies investigating SRS for distant metastases to the base of skull and cavernous sinus

Study	Treatment Modality	Lesion type/ location	Patients, n	Median Prescribed SRS Dose/Fractions, Gy	Median Survival, mo	Symptom Improvement, %	Local Tumor Control, %	Factors Associated With Shorter Survival	Complication Rate, %
Iwai et al. [19]	Gamma Knife	Metastases or invasion/ Cavernous sinus	21	14/1	13 (mean)	48%	67%	Systemic metastases	0%
Mori et al. [20]	Gamma Knife	Metastases/ Cavernous sinus and pituitary	13	15/1	N/A	67%	67%	N/A	8%
Kano et al. [18]	Gamma Knife	Metastases or invasion/ Cavernous sinus	37	14/1	8.9	35%	78%	Older age, systemic metastases	0%
Mori et al. [14]	Linac-based SRS	Metastases/ Base of skull	11	37.8/10	16	91%	100%	N/A	0%
Present Study	Linac-based SRS	Metastases/ Base of skull	18	18/1	1.8	83% (cranial nerves), 100% (pain)	63%	Lower RPA, Lower KPS	12.5%

rate of pain improvement was 100%. Mori et al. [14] similarly found a 91% rate of symptomatic improvement. As skullbase metastases often present with profound and evolving cranial nerve deficits and pain, these high rates of improvement are encouraging and suggest that while overall survival is poor in this cohort, SRS may be a valuable treatment option in the palliative setting. Furthermore, only one patient experienced a low-grade adverse effect related to radiation treatment that resolved with a short course of steroids. Other studies have similarly found complication rates ranging from 0-8% after the use of SRS for base of skull or cavernous sinus metastases and extensions [14,18,19,20].

In contradistinction to Mori et al. [14] who delivered treatment in ≥10 fractions, our patients were managed with 1-5 fractions and attained similar rates of symptomatic improvement and adverse effects. This may be partially related to the fact that their treatment volumes were significantly larger than ours (median tumor volume 61.6 cc vs. 2.9 cc). Given the low rate of adverse neurological effects, our results suggest that neurovascular structures contained in base of skull metastases may be adequately resilient and may not require dosing schemes of greater than 5 fractions. However, given the poor survival of the patients in this cohort, it is possible that developing adverse effects involving cranial nerves did not have sufficient time to manifest. The ability to achieve comparable rates of local control and pain relief with fewer fractions is critical for a patient population that is often hospitalized with evolving local symptoms as well as advanced disease and poor performance status that may not be able to tolerate 10+ daily treatment visits or unnecessarily prolonged hospitalizations. We recognize that the survival of such patients is expected to be short and many will be transitioned to hospice care following treatment. Nevertheless, given the presence of debilitating pain or neurological defects in this cohort, we believe that such patients may benefit from palliative radiotherapy despite short life expectancy. Specifically, we believe that palliative stereotactic radiotherapy may be an appropriate approach in this setting given the fewer number of fractions and shorter treatment time. Patients with severe pain and neurological deficits are likely to benefit most from this treatment.

Limitations of the current study include its retrospective nature that necessitates inherent biases. Despite being the largest linac-based series in the literature looking exclusively at SRS for base of skull metastases, our sample numbers are limited which may have hindered the identification of some prognostic predictors and accurate analysis of outcomes. Furthermore, our patient population is fairly heterogeneous with multiple primary histologies and treatment regimens represented which may further limit the applicability of our findings.

SRS is a safe and potentially effective treatment for skull base metastases with acceptable rates of local control. While this patient population exhibits limited survival secondary to extensive systemic disease, the vast majority of patients are symptomatic at presentation. KPS and RPA measurements may be valuable for predicting outcomes following treatment. Most importantly, SRS leads to improvement in both pain and cranial nerve deficits and should therefore be integrated into the multidisciplinary palliation of this unique patient population.

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